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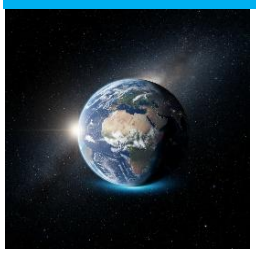

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Monoclonal antibodies against CGRP in migraine prevention: current state of knowledge

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Abstract

Background. Migraine is one of the most common neurological disorders and has a significant impact on patients' quality of life. In recent years, growing attention has been directed toward targeted therapies focused on the calcitonin gene-related peptide (CGRP) pathway, which represent a novel option in migraine prevention.

Aim. The aim of this study was to present the current state of knowledge regarding the use of monoclonal antibodies targeting CGRP in migraine prevention, with particular emphasis on their mechanisms of action, clinical efficacy, and safety profile.

Materials and methods. A narrative literature review was conducted using the PubMed and Scopus databases. Publications from recent years were included, encompassing original

studies, systematic reviews, and meta-analyses addressing anti-CGRP monoclonal antibody therapy in migraine treatment.

Results. Available evidence indicates that monoclonal antibodies targeting the CGRP pathway effectively reduce the number of migraine days and improve patients' quality of life, including in individuals who are resistant to previous preventive therapies. Sustained therapeutic effects have also been observed in long-term follow-up. These therapies are characterized by a favorable safety profile, with adverse events typically being mild in nature. However, the available findings remain partly heterogeneous, and data concerning specific patient populations are still limited.

Conclusions. Anti-CGRP monoclonal antibodies represent an effective and well-tolerated option for the preventive treatment of migraine. Their use may significantly improve disease control, particularly in patients with an inadequate response to previous therapies. However, further studies are required to evaluate long-term safety and to optimize therapeutic strategies.

Keywords: migraine, CGRP, monoclonal antibodies, migraine prevention, erenumab, fremanezumab, galcanezumab, eptinezumab.

1.Introduction

Migraine is one of the most common primary headache disorders of neurological origin. It is characterized by recurrent episodes of headache that may be accompanied by a range of associated symptoms, including nausea, vomiting, and hypersensitivity to sensory stimuli such as light and sound (Ashina, Katsarava, et al., 2021; Imai & Matsumori, 2024). Migraine attacks may vary in intensity and duration; however, in many cases they lead to a significant impairment of daily functioning (Pescador Ruschel & De Jesus, 2026).

The diagnosis of migraine is primarily based on clinical criteria defined in the International Classification of Headache Disorders, 3rd edition (ICHD-3), developed by the International Headache Society. According to this classification, several forms of the disease are distinguished, the most common being migraine without aura and migraine with aura. In the latter, transient neurological symptoms precede the onset of headache, most commonly visual disturbances, and less frequently sensory symptoms or speech disturbances (ICHD-3, 2018). Clinical studies also indicate that the course of migraine may vary considerably between patients, both in terms of attack frequency and the severity of associated symptoms (Torres-Ferrús et al., 2020).

Migraine represents a significant health problem with substantial epidemiological impact. It is estimated to affect approximately one-seventh of the population, making it one of the most common neurological disorders (Dong et al., 2025). It occurs considerably more frequently in women than in men, which is partly attributed to the influence of hormonal factors on the development and course of the disease (Tsai et al., 2022). The highest prevalence is observed in individuals of working age, particularly between 20 and 54 years, which translates into a significant social and economic burden. Studies conducted in European headache centers indicate that a substantial proportion of patients experience frequent migraine attacks requiring preventive treatment (Dong et al., 2025; Pozo-Rosich et al., 2021). At the same time, in some patients, currently available preventive therapies are either ineffective or limited by adverse effects (Buse et al., 2023; Pozo-Rosich et al., 2021).

Despite the availability of multiple therapeutic options, there remains a need for further evaluation of the efficacy and safety of novel targeted therapies, including anti-CGRP monoclonal antibodies, particularly in the context of long-term data and treatment-resistant populations. The aim of this study was to present the current state of knowledge on the use of monoclonal antibodies targeting CGRP in migraine prevention, with particular emphasis on their mechanisms of action, clinical efficacy, and safety profile.

2. Research materials and methods

A narrative literature review was conducted using the PubMed and Scopus databases to identify relevant publications on the use of monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway in migraine prevention. The search included studies published from January 2020 to March 2026. The following keywords and their combinations were used: "migraine," "CGRP," "calcitonin gene-related peptide," "monoclonal antibodies," "erenumab," "fremanezumab," "galcanezumab," "eptinezumab," "migraine prevention," "efficacy," and "safety."

The inclusion criteria comprised original research articles, systematic reviews, narrative reviews, and meta-analyses published in English that addressed the efficacy, safety, or mechanisms of action of anti-CGRP monoclonal antibodies in migraine treatment. Both clinical studies and real-world evidence analyses were considered. Articles not written in English, opinion pieces, conference abstracts, and studies with insufficient methodological information or without available full text were excluded from the analysis.

3. Research results

3.1. Pathophysiology of migraine and the role of CGRP

The mechanisms underlying migraine are complex and involve the interaction between components of the nervous system and vascular processes. A key role in the generation of a migraine attack is played by the trigeminovascular system, which is responsible for transmitting pain signals from the meninges to the central nervous system. Activation of trigeminal nerve fibers leads to the release of various neuropeptides, including calcitonin gene-related peptide (CGRP), substance P, and neurokinin A (Kuburas & Russo, 2023; Pescador Ruschel & De Jesus, 2026). These substances influence both vascular tone and inflammatory processes. Their action leads to vasodilation and increased vascular permeability, a phenomenon referred to as neurogenic inflammation (Pescador Ruschel & De Jesus, 2026).

CGRP is one of the key mediators involved in the pathophysiology of migraine. It is present in the trigeminal ganglion and plays an important role in the functioning of the trigeminovascular system. Released from trigeminal neurons, CGRP acts as a potent vasodilator and is also involved in the transmission of pain signals and the amplification of inflammatory processes (Kuburas & Russo, 2023; Wattiez et al., 2020). An important component of the CGRP pathway is its receptor, which consists of the calcitonin receptor-like receptor (CLR) and receptor activity-modifying protein 1 (RAMP1). The interaction between CGRP and its receptor plays a crucial role in pain transmission and in the enhancement of inflammatory processes within the trigeminovascular system (Wattiez et al., 2020). Sensitization processes also represent an important aspect of migraine pathophysiology. The involvement of CGRP in neurogenic inflammation may lead to peripheral sensitization of nociceptors, while its activity within the central nervous system is associated with increased sensitivity to sensory stimuli, contributing to the persistence of pain (Wattiez et al., 2020).

The role of CGRP in migraine pathophysiology is further supported by clinical data. It has been demonstrated that its concentration significantly increases during a migraine attack compared to the interictal period and subsequently decreases following the resolution of headache (Kamm et al., 2025). Additional evidence indicates that administration of exogenous CGRP may trigger migraine attacks in patients with migraine and may also

be associated with the occurrence of aura symptoms. These observations highlight the importance of this neuropeptide not only in the generation of pain but also in shaping the overall clinical presentation of a migraine attack (Al-Khazali et al., 2023). Understanding the role of CGRP in migraine mechanisms has enabled the development of targeted therapies that block the activity of this neuropeptide or its receptor. This approach represents a significant breakthrough in the preventive treatment of migraine and defines new directions for the development of therapeutic strategies (Ashina, Goadsby, et al., 2021).

3.2. Mechanism of action of anti-CGRP monoclonal antibodies

Monoclonal antibodies targeting CGRP represent a modern form of targeted therapy, whose therapeutic effect results from the selective inhibition of the CGRP pathway, which plays a key role in the pathogenesis of migraine (Cohen et al., 2022). Their mechanism of action is based on neutralizing CGRP activity either by binding the peptide itself or its receptor, leading to the interruption of pain signal transmission within the trigeminovascular system (Muddam et al., 2023). Depending on the molecular mechanism, two main modes of action can be distinguished: binding of the CGRP ligand by monoclonal antibodies (fremanezumab, galcanezumab, eptinezumab) and blockade of the CGRP receptor by erenumab, thereby preventing its activation. Inhibition of the interaction between CGRP and its receptor results in a reduction of neurogenic inflammation and a decrease in vasodilation, both of which play an important role in the development of migraine pain (Cohen et al., 2022). Furthermore, CGRP blockade affects the function of sensory neurons within the trigeminovascular system, reducing their excitability and limiting the transmission of pain signals to the central nervous system (Aditya & Rattan, 2023).

Due to their large molecular size, these antibodies have limited ability to cross the blood–brain barrier; therefore, their effects are primarily exerted in peripheral structures (González-Hernández et al., 2020). The main sites of action include the trigeminal ganglion, the meninges, and meningeal blood vessels, which play a key role in the generation of pain signals (Cohen et al., 2022). An important effect of these agents is the modulation and normalization of peripheral sensitization, leading to reduced hypersensitivity to pain stimuli (Manganotti et al., 2024). Preclinical studies further indicate that CGRP blockade affects the activity of pain-transmitting nerve fibers, particularly through selective inhibition of Aδ fibers, resulting in reduced pain transmission (Cohen et al., 2022). Anti-CGRP monoclonal antibodies are characterized by high specificity and strong affinity for their molecular target,

enabling selective modulation of the CGRP pathway with a low risk of off-target effects (Muddam et al., 2023).

Their pharmacokinetic properties differ from those of conventional drugs, as these antibodies are not subject to hepatic metabolism or renal excretion but are primarily eliminated via the reticuloendothelial system, which is associated with a low risk of drug–drug interactions (Cohen et al., 2022; Muddam et al., 2023). Elimination of monoclonal antibodies occurs mainly through proteolytic catabolism, while the neonatal Fc receptor (FcRn) protects IgG from lysosomal degradation and mediates its recycling, thereby prolonging its half-life (Pyzik et al., 2023). The long half-life (27–31 days) allows for administration in monthly or quarterly dosing regimens, supporting the maintenance of a stable therapeutic effect (Barnes et al., 2025). Treatment with anti-CGRP monoclonal antibodies leads to a significant reduction in the number of migraine days and improves the effectiveness of acute treatment, as demonstrated in real-world studies (Rosignoli et al., 2024).

3.3 Characteristics of available therapies

Currently used and recommended monoclonal antibodies targeting the CGRP pathway for migraine prevention, according to the European Headache Federation (EHF), include erenumab, fremanezumab, galcanezumab, and eptinezumab (Sacco et al., 2022). Individual agents differ in their mechanisms of action, routes of administration, and dosing regimens, which is of significant importance in clinical practice (Hu et al., 2022; McAllister et al., 2022; Sacco et al., 2022).

Erenumab is the only monoclonal antibody that targets the CGRP receptor (Ashina, Goadsby, et al., 2021). It is administered subcutaneously on a monthly basis (Reuter et al., 2022). Clinical studies highlight its distinct adverse event profile compared with antibodies that neutralize the CGRP ligand, which may be relevant for individualized treatment selection (Dodick et al., 2025).

Fremanezumab and galcanezumab are monoclonal antibodies that bind to the CGRP ligand (Hu et al., 2022; Weatherall, 2021). Fremanezumab can be administered either monthly or quarterly, providing greater flexibility in treatment (Weatherall, 2021). Galcanezumab is administered once monthly, with a loading dose at the initiation of therapy (Hu et al., 2022). Both agents are administered subcutaneously and exhibit similar pharmacokinetic properties (La Rocca et al., 2023; Weatherall, 2021).

Eptinezumab, similarly to the other monoclonal antibodies that bind the CGRP ligand, is administered differently - via intravenous infusion at 12-week intervals (McAllister et al.,

2022). This route of administration allows for rapid attainment of therapeutic plasma concentrations, which translates into a fast onset of action (Apelian et al., 2022; McAllister et al., 2022).

Despite a shared therapeutic target, anti-CGRP monoclonal antibodies differ in several practical aspects of their use (Ashina, Goadsby, et al., 2021; Weatherall, 2021). Erenumab, as the only agent that blocks the CGRP receptor, exhibits a distinct adverse event profile compared with other anti-CGRP antibodies (Dodick et al., 2025). Fremanezumab is characterized by flexible dosing options, whereas eptinezumab is distinguished by its intravenous route of administration and rapid onset of action (Apelian et al., 2022; McAllister et al., 2022; Weatherall, 2021). These differences may influence treatment selection and serve as an important consideration in the evaluation of the efficacy and safety of anti-CGRP therapies (Quintana et al., 2022).

3.4 Clinical efficacy of anti-CGRP therapy

The efficacy of monoclonal antibodies targeting the CGRP pathway has been widely documented in clinical studies. Their use is associated with a significant reduction in the number of monthly migraine days, which represents a key goal of preventive treatment (Ashina, Goadsby, et al., 2021; Weatherall, 2021). Studies involving erenumab, fremanezumab, and galcanezumab indicate that a substantial proportion of patients achieve a clinically meaningful improvement, defined as a reduction in monthly migraine days of at least 50%. In some analyses, even higher response rates have been observed, further supporting the high efficacy of this therapeutic class (Driessen et al., 2022; Hu et al., 2022; Reuter et al., 2022). Anti-CGRP monoclonal antibodies have also demonstrated efficacy in patients with chronic migraine and in those who did not respond to previous preventive treatments. In these populations, significant reductions in the number of migraine days, as well as improvements in daily functioning, have been reported, highlighting their value in treatment-resistant patients (Lipton et al., 2025; Pozo-Rosich et al., 2024). Long-term studies, including those involving erenumab, indicate that the therapeutic effect is maintained over time without significant loss of efficacy. Sustained reductions in attack frequency have been observed during prolonged treatment, which is particularly important in the management of a chronic condition such as migraine (Reuter et al., 2024).

Beyond the reduction in attack frequency, anti-CGRP therapy also has a beneficial impact on patients' quality of life. Studies involving galcanezumab have demonstrated a reduction in pain intensity and a decreased impact of the disease on daily functioning

(La Rocca et al., 2023; Lipton et al., 2023). Furthermore, this treatment is associated with a reduced need for acute medication, including drugs used for the termination of migraine attacks (La Rocca et al., 2023).

Another important aspect is the rapid onset of action. In the PROMISE-2 study, the preventive effect of eptinezumab was observed early in the course of treatment, with a significant reduction in migraine frequency already evident from the first day after administration. This was further confirmed by a lower proportion of patients experiencing migraine on the day following infusion (Lipton et al., 2020).

Data from real-world clinical practice confirm that the efficacy observed in randomized trials is reflected in everyday clinical settings. A significant and sustained reduction in the number of migraine days, as well as improvements in quality of life, have been reported, including in patients with previous treatment failures (Buse et al., 2023; Dodick et al., 2025). Available evidence suggests comparable efficacy among anti-CGRP monoclonal antibodies, with observed differences having limited clinical relevance. In clinical practice, this underscores the importance of individualized treatment and tailoring therapy selection to the characteristics of each patient (Quintana et al., 2022).

3.5. Safety profile

Monoclonal antibodies targeting the CGRP pathway demonstrate a favorable safety profile, as evidenced by both clinical trials and analyses conducted in real-world settings (Barbanti et al., 2025; Mascarella et al., 2024; Reuter et al., 2022). Real-world data indicate that anti-CGRP monoclonal antibodies are generally well tolerated, with adverse events typically being mild in nature (Muñoz-Vendrell et al., 2023). Importantly, their favorable safety profile appears to be maintained over time and is not associated with a significant increase in the frequency of adverse events (Barbanti et al., 2025; Lo Castro et al., 2025).

Observational studies have reported that adverse events include constipation, dizziness, and injection site reactions (Muñoz-Vendrell et al., 2023). In the case of erenumab, constipation has been identified as one of the more common adverse events and may occur more frequently than in the placebo group (Yu et al., 2022). Eptinezumab, administered intravenously, is associated with a distinct safety profile, primarily related to the risk of hypersensitivity reactions during infusion, such as flushing, rash, or pruritus. These events are generally mild to moderate in severity and tend to resolve spontaneously, while the incidence of serious adverse events remains low and comparable to placebo (T. R. Smith et al., 2021).

Despite the overall good tolerability of these therapies, data on the safety of anti-CGRP monoclonal antibodies remain limited in specific populations, such as pregnant women, elderly individuals, and patients with severe cardiovascular diseases (Cohen et al., 2022; Yang et al., 2025).

4. Discussion

Monoclonal antibodies targeting the CGRP pathway represent a modern option for migraine prevention, with particular relevance for patients in whom previous treatment strategies have been ineffective or poorly tolerated (Barbanti et al., 2025; Muñoz-Vendrell et al., 2023). Their therapeutic effect is based on modulation of one of the key pathophysiological mechanisms of migraine, allowing for a more precise intervention compared with traditional preventive treatments (Wattiez et al., 2020). Clinical trial results and real-world data consistently demonstrate a significant reduction in migraine attack frequency and an improvement in patient functioning, while maintaining a favorable safety profile (Buse et al., 2023; Muñoz-Vendrell et al., 2023). Available analyses also suggest no significant differences in efficacy between individual agents, which highlights the importance of an individualized approach to treatment selection (Quintana et al., 2022).

On the other hand, several limitations of the current evidence should be considered, including the relatively short duration of follow-up and the insufficient representation of specific patient populations (Lo Castro et al., 2025; Yang et al., 2025). Additionally, the heterogeneity of available studies, resulting from differences in study design, inclusion criteria, and applied endpoints, may hinder direct comparisons of the efficacy of individual agents (Quintana et al., 2022). Another important limitation of anti-CGRP therapy is its high cost and the associated restrictions in treatment accessibility, which influence patient eligibility criteria and reimbursement policies (A. Smith et al., 2024). Consequently, further research should focus on the evaluation of long-term safety and the identification of factors determining treatment response, which may support the development of more individualized therapeutic strategies (Lo Castro et al., 2025).

5. Conclusions

Monoclonal antibodies targeting the CGRP pathway represent a modern and effective option for the preventive treatment of migraine, with particular benefit for patients in whom previous therapies have been ineffective or poorly tolerated. Their mechanism of action, based on selective modulation of key elements of migraine pathophysiology, translates into

a significant reduction in attack frequency and improvement in patient functioning. Available data indicate comparable efficacy among individual agents, highlighting the importance of individualized treatment selection based on patient-specific clinical characteristics. Despite their favorable safety profile, further data are required to assess long-term use and their application in specific patient populations.

Disclosure

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Declaration of the use of generative AI and AI-assisted technologies in the writing process

In preparing this work, the author(s) used ChatGPT for language improvement and grammatical correction. After using this tool/service, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

References

Aditya, S., & Rattan, A. (2023). Advances in CGRP monoclonal antibodies as migraine therapy: A narrative review. *Saudi Journal of Medicine and Medical Sciences*, *11*(1), 11–18. https://doi.org/10.4103/sjmms.sjmms_95_22

Al-Khazali, H. M., Ashina, H., Wiggers, A., Rose, K., Iljazi, A., Christensen, R. H., Schytz, H. W., Amin, F. M., & Ashina, M. (2023). Calcitonin gene-related peptide causes migraine aura. *The Journal of Headache and Pain*, *24*(1), 124. https://doi.org/10.1186/s10194-023-01656-4

Apelian, R., Boyle, L., Hirman, J., & Asher, D. (2022). Measuring dose-related efficacy of eptinezumab for migraine prevention: post hoc analysis of PROMISE-1 and PROMISE-2. *The Journal of Headache and Pain*, *23*(1), 48. https://doi.org/10.1186/s10194-022-01418-8

Ashina, M., Goadsby, P. J., Reuter, U., Silberstein, S., Dodick, D. W., Xue, F., Zhang, F., Paiva da Silva Lima, G., Cheng, S., & Mikol, D. D. (2021). Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial. *European Journal of Neurology*, *28*(5), 1716–1725. https://doi.org/10.1111/ene.14715

Ashina, M., Katsarava, Z., Do, T. P., Buse, D. C., Pozo-Rosich, P., Özge, A., Krymchantowski, A. V., Lebedeva, E. R., Ravishankar, K., Yu, S., Sacco, S., Ashina, S., Younis, S., Steiner, T. J., & Lipton, R. B. (2021). Migraine: epidemiology and systems of care. *The Lancet*, *397*(10283), 1485–1495. https://doi.org/10.1016/S0140-6736(20)32160-7

Barbanti, P., Aurilia, C., Egeo, G., Doretti, A., d'Onofrio, F., Scatena, P., Rinalduzzi, S., Vinciguerra, L., Sansone, M., Vecchio, R., Drago, V., Viticchi, G., Bartolini, M., Ranieri, A., Bandettini di Poggio, M., Baldisseri, F., Mascarella, D., Brusaferri, F., Caputi, L., … Italian Migraine Registry (I-GRAINE) study group. (2025). A 24-week prospective, multicenter, real-world study on eptinezumab's effectiveness and safety in migraine prevention (EMBRACE II). *Journal of Neurology*, *272*(6), 382. https://doi.org/10.1007/s00415-025-13095-z

Barnes, S., Aldous, L., & Jenkins, B. (2025). Calcitonin gene-related peptide-targeted therapies for migraine. *Australian Prescriber*, *48*(2), 40–46. https://doi.org/10.18773/austprescr.2025.017

Buse, D. C., Pozo-Rosich, P., Dupont-Benjamin, L., Balkaran, B. L., Lee, L., Jauregui, A., Gandhi, P., Parikh, M., & Reuter, U. (2023). Impact of headache frequency and preventive medication failure on quality of life, functioning, and costs among individuals with migraine across several European countries: need for effective preventive treatment. *The Journal of Headache and Pain*, *24*(1), 115. https://doi.org/10.1186/s10194-023-01655-5

Cohen, F., Yuan, H., DePoy, E. M. G., & Silberstein, S. D. (2022). The Arrival of Anti-CGRP Monoclonal Antibodies in Migraine. *Neurotherapeutics*, *19*(3), 922–930. https://doi.org/10.1007/s13311-022-01230-x

Dodick, D. W., Tepper, S. J., Ailani, J., Khodavirdi, A. C., Pannacciulli, N., Fu, A., Kent, S. T., Gill, K., Urman, R., & Oh, S. S. (2025). Effect of erenumab versus other migraine preventive medications on cardiovascular and cerebrovascular outcomes: A United States claims database-based observational cohort study. *Headache*, *65*(6), 919–932. https://doi.org/10.1111/head.14912

Dong, L., Dong, W., Jin, Y., Jiang, Y., Li, Z., & Yu, D. (2025). The Global Burden of Migraine: A 30-Year Trend Review and Future Projections by Age, Sex, Country, and Region. *Pain and Therapy*, *14*(1), 297–315. https://doi.org/10.1007/s40122-024-00690-7

Driessen, M. T., Cohen, J. M., Thompson, S. F., Patterson-Lomba, O., Seminerio, M. J., Carr, K., Totev, T. I., Sun, R., Yim, E., Mu, F., & Ayyagari, R. (2022). Real-world effectiveness after initiating fremanezumab treatment in US patients with episodic and chronic migraine or difficult-to-treat migraine. *The Journal of Headache and Pain*, *23*(1), 56. https://doi.org/10.1186/s10194-022-01415-x

González-Hernández, A., Marichal-Cancino, B. A., García-Boll, E., & Villalón, C. M. (2020). The locus of Action of CGRPergic Monoclonal Antibodies Against Migraine: Peripheral Over Central Mechanisms. *CNS & Neurological Disorders Drug Targets*, *19*(5), 344–359. https://doi.org/10.2174/1871527319666200618144637

Hu, B., Li, G., Li, X., Wu, S., Yu, T., Li, X., Zhao, H., Jia, Z., Zhuang, J., & Yu, S. (2022). Galcanezumab in episodic migraine: the phase 3, randomized, double-blind, placebo-controlled PERSIST study. *The Journal of Headache and Pain*, *23*(1), 90. https://doi.org/10.1186/s10194-022-01458-0

ICHD-3. (2018). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*, *38*(1), 1–211. https://doi.org/10.1177/0333102417738202

Imai, N., & Matsumori, Y. (2024). Different effects of migraine associated features on headache impact, pain intensity, and psychiatric conditions in patients with migraine. *Scientific Reports*, *14*(1), 22611. https://doi.org/10.1038/s41598-024-74253-3

Kamm, K., Brandi-Dohrn, A., Straube, A., Förderreuther, S., & Ruscheweyh, R. (2025). Tear fluid calcitonin gene-related peptide (CGRP) is elevated during spontaneous migraine attacks - results from a pilot study. *The Journal of Headache and Pain*, *27*(1), 31. https://doi.org/10.1186/s10194-025-02255-1

Kuburas, A., & Russo, A. F. (2023). Shared and independent roles of CGRP and PACAP in migraine pathophysiology. *The Journal of Headache and Pain*, *24*(1), 34. https://doi.org/10.1186/s10194-023-01569-2

La Rocca, M., Laporta, A., Clemente, L., Ammendola, E., Delussi, M. D., Ricci, K., Tancredi, G., Stramaglia, S., & de Tommaso, M. (2023). Galcanezumab treatment changes visual related EEG connectivity patterns in migraine patients. *Cephalalgia*, *43*(8), 3331024231189751. https://doi.org/10.1177/03331024231189751

Lipton, R. B., Buse, D. C., Sandoe, C. H., Ford, J. H., Hand, A. L., Jedynak, J. P., Port, M. D., & Detke, H. C. (2023). Changes in migraine interictal burden following treatment with galcanezumab: Results from a phase III randomized, placebo-controlled study. *Headache*, *63*(5), 683–691. https://doi.org/10.1111/head.14460

Lipton, R. B., Goadsby, P. J., Smith, J., Schaeffler, B. A., Biondi, D. M., Hirman, J., Pederson, S., Allan, B., & Cady, R. (2020). Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology*, *94*(13), e1365–e1377. https://doi.org/10.1212/WNL.0000000000009169

Lipton, R. B., Ramirez Campos, V., Roth-Ben Arie, Z., Galic, M., Mitsikostas, D., Tassorelli, C., Denysenko, L., & Cohen, J. M. (2025). Fremanezumab for the treatment of patients with migraine and comorbid major depressive disorder: the UNITE randomized clinical trial. *JAMA Neurology*, *82*(6), 560–569. https://doi.org/10.1001/jamaneurol.2025.0806

Lo Castro, F., Bonini, N., Iannone, L. F., Boccalini, A., Brovia, D., Pani, L., Boriani, G., & Guerzoni, S. (2025). No Increase in Blood Pressure Assessed With the 24-h Holter Monitoring in Patients With Episodic Migraine During Early Treatment With Anti-CGRP Monoclonal Antibodies: A Prospective Observational Study (SAFHYPER). *European Journal of Neurology*, *32*(9), e70351. https://doi.org/10.1111/ene.70351

Manganotti, P., Deodato, M., D'Acunto, L., Biaduzzini, F., Garascia, G., & Granato, A. (2024). Effects of Anti-CGRP Monoclonal Antibodies on Neurophysiological and Clinical

Outcomes: A Combined Transcranial Magnetic Stimulation and Algometer Study. *Neurology International*, *16*(4), 673–688. https://doi.org/10.3390/neurolint16040051

Mascarella, D., Andrini, G., Baraldi, C., Altamura, C., Favoni, V., Lo Castro, F., Pierangeli, G., Vernieri, F., Guerzoni, S., & Cevoli, S. (2024). Blood pressure monitoring in elderly migraineurs starting an anti-CGRP monoclonal antibody: a real-world prospective study. *Neurological Sciences*, *45*(11), 5365–5373. https://doi.org/10.1007/s10072-024-07567-9

McAllister, P., Kudrow, D., Cady, R., Hirman, J., & Ettrup, A. (2022). Reduction in migraine-associated burden after eptinezumab treatment in patients with chronic migraine. *Cephalalgia*, *42*(10), 1005–1012. https://doi.org/10.1177/03331024221089567

Muddam, M. R., Obajeun, O. A., Abaza, A., Jaramillo, A. P., Sid Idris, F., Anis Shaikh, H., Vahora, I., Moparthi, K. P., Al Rushaidi, M. T., & Nath, T. S. (2023). Efficacy and Safety of Anti-calcitonin Gene-Related Peptide (CGRP) Monoclonal Antibodies in Preventing Migraines: A Systematic Review. *Cureus*, *15*(9), e45560. https://doi.org/10.7759/cureus.45560

Muñoz-Vendrell, A., Campoy, S., Caronna, E., Alpuente, A., Torres-Ferrus, M., Nieves Castellanos, C., Olivier, M., Campdelacreu, J., Prat, J., Camiña Muñiz, J., Molina Martínez, F. J., Mínguez-Olaondo, A., Ruibal Salgado, M., Santos Lasaosa, S., Navarro Pérez, M. P., Morollón, N., López Bravo, A., Cano Sánchez, L. M., García-Sánchez, S. M., … Huerta-Villanueva, M. (2023). Effectiveness and safety of anti-CGRP monoclonal antibodies in patients over 65 years: a real-life multicentre analysis of 162 patients. *The Journal of Headache and Pain*, *24*(1), 63. https://doi.org/10.1186/s10194-023-01585-2

Pescador Ruschel, M. A., & De Jesus, O. (2026). Migraine Headache. In *StatPearls*. StatPearls Publishing.

Pozo-Rosich, P., Dolezil, D., Paemeleire, K., Stepien, A., Stude, P., Snellman, J., Arkuszewski, M., Stites, T., Ritter, S., Lopez Lopez, C., Maca, J., Ferraris, M., & Gil-Gouveia, R. (2024). Early use of erenumab vs nonspecific oral migraine preventives: the APPRAISE randomized clinical trial. *JAMA Neurology*, *81*(5), 461–470. https://doi.org/10.1001/jamaneurol.2024.0368

Pozo-Rosich, P., Lucas, C., Watson, D. P. B., Gaul, C., Ramsden, E., Ritter, S., Martelletti, P., & Snellman, J. (2021). Burden of Migraine in Patients With Preventive Treatment Failure Attending European Headache Specialist Centers: Real-World Evidence From the BECOME Study. *Pain and Therapy*, *10*(2), 1691–1708. https://doi.org/10.1007/s40122-021-00331-3

Pyzik, M., Kozicky, L. K., Gandhi, A. K., & Blumberg, R. S. (2023). The therapeutic age of the neonatal Fc receptor. *Nature Reviews. Immunology*, *23*(7), 415–432. https://doi.org/10.1038/s41577-022-00821-1

Quintana, S., Russo, M., Manzoni, G. C., & Torelli, P. (2022). Comparison study between erenumab, fremanezumab, and galcanezumab in the preventive treatment of high frequency episodic migraine and chronic migraine. *Neurological Sciences*, *43*(9), 5757–5758. https://doi.org/10.1007/s10072-022-06254-x

Reuter, U., Ehrlich, M., Gendolla, A., Heinze, A., Klatt, J., Wen, S., Hours-Zesiger, P., Nickisch, J., Sieder, C., Hentschke, C., & Maier-Peuschel, M. (2022). Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. *Cephalalgia*, *42*(2), 108–118. https://doi.org/10.1177/03331024211053571

Reuter, U., Heinze, A., Gendolla, A., Sieder, C., & Hentschke, C. (2024). Erenumab versus topiramate: migraine-related disability, impact and health-related quality of life. *European Journal of Neurology*, *31*(12), e16437. https://doi.org/10.1111/ene.16437

Rosignoli, C., Caponnetto, V., Onofri, A., Trozzi, V., Tartaglione, L., Silvestro, M., Russo, A., Sacco, S., & Ornello, R. (2024). Monoclonal antibodies targeting the calcitonin gene-related peptide pathway improve the effectiveness of acute medication-a real-world study. *Neurological Sciences*, *45*(7), 3305–3312. https://doi.org/10.1007/s10072-024-07380-4

Sacco, S., Amin, F. M., Ashina, M., Bendtsen, L., Deligianni, C. I., Gil-Gouveia, R., Katsarava, Z., MaassenVanDenBrink, A., Martelletti, P., Mitsikostas, D.-D., Ornello, R., Reuter, U., Sanchez-Del-Rio, M., Sinclair, A. J., Terwindt, G., Uluduz, D., Versijpt, J., & Lampl, C. (2022). European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. *The Journal of Headache and Pain*, *23*(1), 67. https://doi.org/10.1186/s10194-022-01431-x

Smith, A., Finnigan, K., Clarke, S., Barry, M., & Gorry, C. (2024). Utilization, Expenditure, and Treatment Patterns Associated With Calcitonin Gene-Related Peptide Monoclonal Antibodies Reimbursed Subject to a Managed Access Protocol in Ireland. *Value in Health*, *27*(8), 1039–1045. https://doi.org/10.1016/j.jval.2024.04.002

Smith, T. R., Spierings, E. L. H., Cady, R., Hirman, J., Schaeffler, B., Shen, V., Sperling, B., Brevig, T., Josiassen, M. K., Brunner, E., Honeywell, L., & Mehta, L. (2021). Safety and tolerability of eptinezumab in patients with migraine: a pooled analysis of 5 clinical trials. *The Journal of Headache and Pain*, *22*(1), 16. https://doi.org/10.1186/s10194-021-01227-5

Torres-Ferrús, M., Ursitti, F., Alpuente, A., Brunello, F., Chiappino, D., de Vries, T., Di Marco, S., Ferlisi, S., Guerritore, L., Gonzalez-Garcia, N., Gonzalez-Martinez, A., Khutorov, D., Kritsilis, M., Kyrou, A., Makeeva, T., Minguez-Olaondo, A., Pilati, L., Serrien, A., Tsurkalenko, O., … School of Advanced Studies of European Headache Federation (EHF-SAS). (2020). From transformation to chronification of migraine: pathophysiological and clinical aspects. *The Journal of Headache and Pain*, *21*(1), 42. https://doi.org/10.1186/s10194-020-01111-8

Tsai, C.-K., Tsai, C.-L., Lin, G.-Y., Yang, F.-C., & Wang, S.-J. (2022). Sex differences in chronic migraine: focusing on clinical features, pathophysiology, and treatments. *Current Pain and Headache Reports*, *26*(5), 347–355. https://doi.org/10.1007/s11916-022-01034-w

Wattiez, A.-S., Sowers, L. P., & Russo, A. F. (2020). Calcitonin gene-related peptide (CGRP): role in migraine pathophysiology and therapeutic targeting. *Expert Opinion on Therapeutic Targets*, *24*(2), 91–100. https://doi.org/10.1080/14728222.2020.1724285

Weatherall, M. W. (2021). Fremanezumab autoinjector pen for the prevention of migraine. *Therapeutic Delivery*, *12*(9), 645–650. https://doi.org/10.4155/tde-2021-0028

Yang, S., Orlova, Y., Park, H., Smith, S. M., Guo, Y., Chapin, B. A., Wilson, D. L., & Lo-Ciganic, W.-H. (2025). Cardiovascular Safety of Anti-CGRP Monoclonal Antibodies in Older Adults or Adults With Disability With Migraine. *JAMA Neurology*, *82*(2), 132–141. https://doi.org/10.1001/jamaneurol.2024.4537

Yu, S., Kim, B.-K., Wang, H., Zhou, J., Wan, Q., Yu, T., Lian, Y., Arkuszewski, M., Ecochard, L., Wen, S., Yin, F., Li, Z., Su, W., & Wang, S.-J. (2022). A phase 3, randomised, placebo-controlled study of erenumab for the prevention of chronic migraine in patients from Asia: the DRAGON study. *The Journal of Headache and Pain*, *23*(1), 146. https://doi.org/10.1186/s10194-022-01514-9